# Immunomorphologic Characterization of FcεRI-Bearing Cells Within the Human Dermis

Birgit Osterhoff, Klemens Rappersberger,* Binghe Wang, Frieder Koszik, Kenichi Ochiai,† Jean-Pierre Kinet,† and Georg Stingl

Department of Dermatology, Division of Immunology, Allergy & Infectious Diseases and *Division of General Dermatology, University of Vienna Medical School and Vienna International Research Cooperation Center (VIRCC), Vienna, Austria; and †Molecular Allergy and Immunology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland, U.S.A.

Recently we reported that the high-affinity receptor for IgE, FcεRI, is constitutively expressed on normal epidermal Langerhans cells (LC) and on certain cells within the dermis. To study the nature of these cells we performed immunofluorescence double-labeling experiments using an anti-FcεRI reagent (MoAb 15-1) as well as monoclonal antibodies (MoAb) against leukocyte differentiation antigens expressed on LC, interdigitating cells and macrophages. Avidin-fluorescein isothiocyanate was used to distinguish mast cells.

We found that dermal FcεRI$^+$ cells are bone marrow derived (CD45$^+$). Further, we found that a subset of 15-1$^+$ dermal cells coexpresses antigens present on certain members of the LC/DC family: the majority of FcεRI$^+$ cells reacted with MoAb anti-HLA-DR and RFD1, the latter recognizes an antigenic moiety on interdigitating cells, and a small subpopulation coexpressed CD1a. In reverse fashion, virtually all CD1a$^+$ cells and most RFD1$^+$ cells reacted with the anti-FcεRI reagent. Approximately one third of 15-1$^+$ cells represented avidin-FITC$^+$ mast cells whereas FcεRI expression was not detected on FXIIIa$^+$ dermal dendrocytes or CD3$^+$ lymphocytes. By immunoelectronmicroscopy, we found that perivascularly located 15-1-reactive cells exhibited pronounced dendrites, an indented nucleus, numerous mitochondria, and abundant endo-/lysosomal structures. However, Birbeck granules or granules specific for basophils or eosinophils were never detected in these cells.

Collectively, our data suggest that the pool of dermal FcεRI$^+$ cells consists mainly of cells of the LC (CD1a$^+$)/DC(RFD1$^+$) lineage and mast cells but does not include FXIIIa$^+$ dermal macrophages. *J Invest Dermatol 102:315–320, 1994*

Recently, we and others [1–3] showed that the high-affinity receptor for IgE (FcεRI) is constitutively expressed on epidermal Langerhans cells (LC) and on certain cells in the dermis that are preferentially located in close proximity to the microvasculature. Some of these cells showed reactivity with fluorescein isothiocyanate (FITC)-labeled avidin and were therefore identified as mast cells [4]. However, a considerable portion of FcεRI$^+$ dermal cells exhibited immunomorphologic features that argued against a mast cells nature, i.e., they were highly dendritic and failed to react with avidin-FITC.

We therefore considered the possibility that a portion of FcεRI$^+$ dermal dendritic‡ cells could be related to cells of the LC/dendritic cell (DC) lineage [5] or to the population of factor XIIIa$^+$ (FXIIIa) dermal dendrocytes that are thought to belong to the mononuclear phagocyte system [6–8] or, even, to non-hematopoietic dendritic cells. To address this issue, we performed immunoelectronmicroscopic studies using the monoclonal antibody (MoAb) 15-1 directed against the α-chain of the FcεRI (FcεRIα) as well as immunofluorescence double-labeling experiments using MoAb 15-1 versus a panel of antibodies directed against several leukocyte differentiation antigens.

## MATERIALS AND METHODS

**Specimen Collection** Specimens of clinically normal-appearing perilesional skin from various anatomical sites were obtained from 10 patients undergoing incisional or excisional biopsies for inflammatory or neoplastic skin conditions.

**Preparation of Tissue** For light microscopic immunolabeling studies, pieces of fresh skin were embedded in Tissue-Tek II OCT (Miles Laboratory Inc., Elkhart, IN), frozen in isopentane cooled in a bath of liquid nitrogen, and stored at −20°C. Four-micrometer cryostat sections were cut and mounted on poly-L-lysine-coated (Sigma, St. Louis, MO) slides. The slides were air-dried, fixed in cold (4°C) acetone for 10 min, and stored at −20°C until use.

For ultrastructural investigations, skin biopsy specimens were cut into small cubes and immediately fixed in paraformaldehyde-lysine-periodate for 5 h at room temperature (RT) [9]. The tissue was then transferred to phosphate-buffered saline (PBS)/10% dimethylsulfoxide (DMSO) and incubated for 1 h at 20°C, before being snap frozen and stored in liquid nitrogen.

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Binghe Wang's present address: Department of Dermatology, First Affiliated Hospital, Nanjing Medical College, Nanjing, P.R. China.

Reprint requests to: Birgit Osterhoff, A.B., DIAID, Department of Dermatology, University of Vienna Medical School, VIRCC, Vienna International Research Cooperation Center, Brunner Strasse 59, A-1235 Vienna, Austria.

Abbreviations: ABC, avidin-biotin complex; FcεRIα, α-chain of the high affinity receptor for IgE; FXIIIa, factor XIIIa.

‡ If not stated differently, we use the term "dendritic" in this study as description of cell morphology independent of its function.

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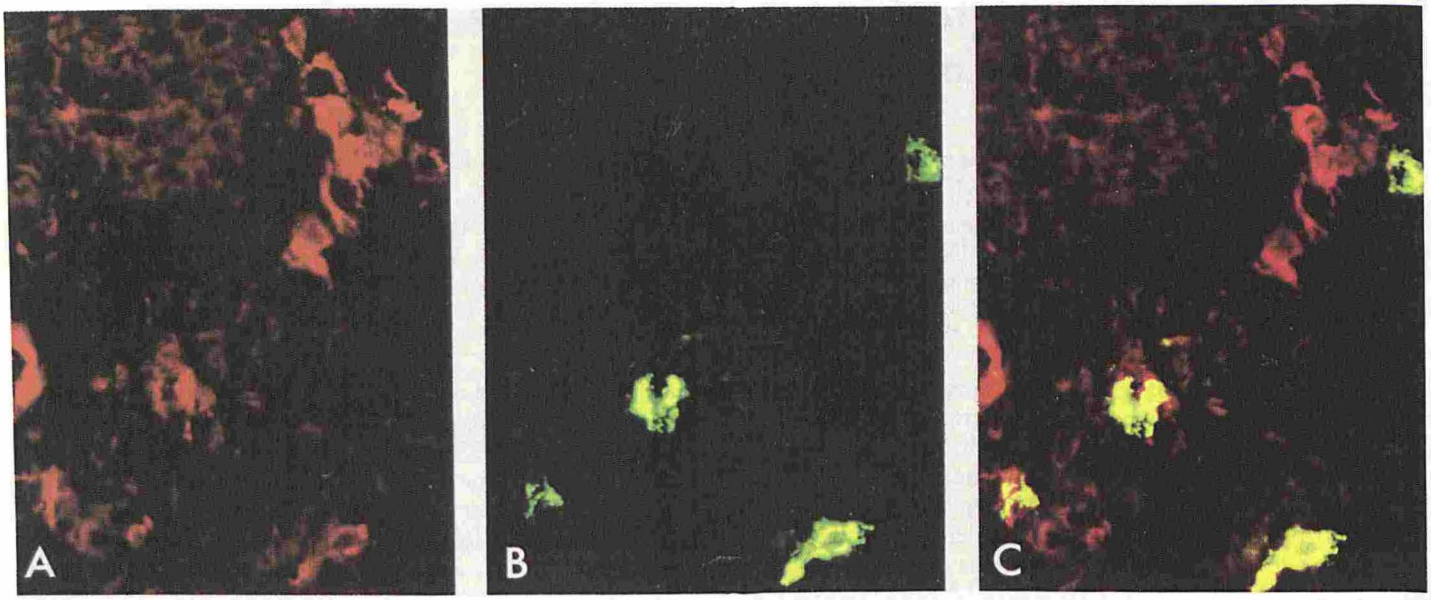


**Figure 1.** Demonstration of FcεRIα$^+$ on dermal mast cells. Cryostat sections were reacted with MoAb 15-1/Texas Red and counterstained with avidin-FITC. Single photographic exposure of an identical field with the appropriate filter shows FcεRIα$^+$ cells in red *(A)* and avidin-FITC$^+$ cells in green *(B)*. Double photographic exposure reveals that some dermal cells appear yellow due to their reactivity with MoAb 15-1 and avidin-FITC *(C)*, demonstrating that these cells are FcεRIα$^+$ mast cells. *Bar*, 24 μm.

**Antibodies** Primary antibodies used are listed in Table I.

**Immunoperoxidase Single-Labeling Procedure** After exposure to 10% sheep serum and 1% human AB serum for 40 min at RT, cryostat sections were incubated overnight with MoAb 15-1 at 4°C. Sections were then consecutively incubated with biotinylated-sheep-F(ab′)$_2$ anti-mouse-Ig (0.6 μg/ml, Amersham Int., Little Chalfont, UK) for 1 h, with avidin-biotin complex (ABC) as indicated by the manufacturer (Dako A/S, Glostrup, Denmark), with 3-amino-9-ethylcarbazole (Sigma) in 0.05 M acetate buffer, pH 5.0, for 5–15 min and, finally, counterstained with hematoxylin.

**Immunofluorescence Double-Labeling Procedures** After exposure to 10% sheep serum for 1 h at RT, cryostat sections were incubated overnight at 4°C with one of the primary MoAb (15-1, KiM8, or IOT6c; all mouse IgG$_1$). To visualize the bound MoAb, sections were further incubated with biotinylated goat-anti-mouse-IgG$_1$ (0.6 μg/ml, Amersham) for 1 h at RT, followed by an incubation with Texas-Red-labeled streptavidin (2.5 μg/ml, Amersham) for 1 h at RT. Sections were then subjected to one of the following counterstaining protocols: a) overnight exposure to FITC-labeled MoAb (see Table I) at 4°C after pre-incubation with 10% normal mouse serum for 40 min; b) incubation with polyclonal rabbit antibody against FXIIIa or CD3 (epsilon chain) overnight at 4°C followed by FITC-labeled swine-anti-rabbit (1:100, Dako A/S) for 1 h at RT; c) incubation with MoAb RFD1 or LeuM1 (both mouse IgM) overnight at 4°C followed by FITC-labeled rat-anti-mouse IgM, 1 μg/ml (Southern Biotechnology Associates, Inc., Birmingham, AL); d) incubation with FITC-conjugated avidin for 2 h at RT to identify mast cells (1:50, Zymed Laboratories Inc., San Francisco, CA) [4].

This basic staining protocol was modified in certain instances to enhance the staining intensity. a) In most experiments biotinylated sheep-F(ab′)$_2$-anti-mouse-Ig (0.6 μg/ml, Amersham) was used in addition to goat-anti-mouse-IgG$_1$ as second-step antibody. b) The incubation chain for visualization of primary mouse antibody was prolonged by the following consecutive incubation steps: biotinylated mouse-IgG$_1$-control-MoAb (1 μg/ml, Coulter Immunology, Hialeah, FL) for 40 min at RT, biotinylated goat-anti-mouse-IgG$_1$ (0.6 μg/ml, Amersham) for 40 min at RT and, finally, with Texas Red-labeled streptavidin (2.5 μg/ml, Amersham) for 40 min at RT. c) FITC-counterstaining was enhanced by the exposure of cryostat

**Table I.** Primary Antibodies Used

| Antibody | Specificity | Species/Isotype | Label | Working Concentration/ Dilution | Source[a] |
|---|---|---|---|---|---|
| 15-1 | FcεRIα | Mouse/IgG$_1$ | | 1.4 μg/ml | J.P. Kinet [1] |
| HLe-1 | CD45 | Mouse/IgG$_1$ | FITC | 0.5 μg/ml | B.D. |
| Anti-HLA-DR | HLA-DR | Mouse/IgG$_{2a}$ | FITC | 0.3 μg/ml | B.D. |
| OKT6 | CD1a | Mouse/IgG$_1$ | FITC | 2.5 μg/ml | Ortho |
| IOT6 | CD1a | Mouse/IgG$_1$ | | 0.2 μg/ml | Immunotech |
| IOT6c | CD1c | Mouse/IgG$_1$ | | 10 μg/ml | Immunotech |
| RFD1 | interdigitating cells | Mouse/IgM | | 1:10 | L.W. Poulter [9] |
| Anti-FxIIIa | FXIIIa | Rabbit polyclonal Ab | | 1:800 | Behring |
| KiM8 | macrophages | Mouse/IgG$_1$ | | 0.2 μg/ml | Behring |
| LeuM1 | CD15 | Mouse/IgM | | 0.5 μg/ml | B.D. |
| Anti-CD3 | CD3 (epsilon chain) | Rabbit polyclonal Ab | | 5 μg/ml | Dako A/S |
| Leu12 | CD19 | Mouse/IgG$_1$ | FITC | 2.5 μg/ml | B.D. |

[a]B.D., Becton Dickinson (Mountain View, CA); Ortho (Raritan, NJ); Immunotech (Marseille, France); Behring, Behringwerke (Marburg/Lahn, Germany); Dako A/S (Glostrup, Denmark).

**Table II.** Expression of Various Leukocyte Differentiation Antigens on FcεRIα$^+$ Dermal Cells[a]

| | |
|---|---|
| CD45 | 98% ± 5% |
| HLA-DR | 84% ± 13% |
| Avidin-FITC | 35% ± 21% |
| CD1a | 14% ± 8% |
| Anti-RFD1 | 72% ± 23% |
| FXIIIa | 0%[b] |
| CD3 | 0% |

[a] Percentage ± SD positive cells out of all FcεRIα$^+$ cells.
[b] In about 5% of FXIIIa$^+$ cells the lack of expression of FcεRIα was ambiguous.

sections to rabbit–anti-FITC (1 : 100, Dako A/S) for 1 h at RT, followed by an incubation with FITC-labeled swine–anti-rabbit (1 : 100, Dako A/S) for 1 h at RT.

All staining reagents were diluted in PBS containing 5% milk proteins. Sections were incubated in a humidified environment. Tris-buffered saline (TBS), pH 7.4, was used as rinsing buffer after each incubation step. After the last incubation step the preparations were covered with polyvinyl alcohol (Hoechst, Frankfurt/Main, Germany) and examined using a microscope (Nikon, Tokyo, Japan) with epifluorescent illumination and selective filters for FITC and Texas Red. Controls were performed by the substitution of primary antibody and/or antibody of the counterstaining procedure with the appropriate isotype control antibody, or with normal rabbit serum. In no case were signals above background levels detected.

The density of positive cells was determined in 8–10 sequential fields of the mid and upper dermis at a 400× magnification (total area equivalent to 2.4–3.0 mm$^2$). The data were then calculated for an area of 1 mm$^2$. By counting the total number of cells positive for each antibody and those that were double-labeled, the proportion of cells bearing both markers were quantified.

**Immunoelectronmicroscopy Studies** Ten- to fifteen-micrometer cryostat sections of paraformaldehyde-lysine-periodate–fixed tissue were subjected to an immunogold staining procedure using a pre-embedding method as described previously [11]. Briefly, sections were quenched in phosphate-buffered saline (PBS)/1% egg albumin (Sigma)/0.005% saponin (Sigma) and then incubated with MoAb 15-1 (14 μg/ml in PBS/0.1% egg albumin/0.005% saponin) for 12 h at 4°C. After washing, the sections were reacted with a 1:5 diluted goat–anti-mouse IgG-gold conjugate (5 nm; Amersham), washed, and fixed with 1.5% glutardialdehyde in 0.1 M cacodylate buffer, pH 7.4. After incubation in veronal acetate-buffered osmium and 0.5% aqueous uranylacetate, the sections were dehydrated and embedded in Epon 812. In control experiments, the MoAb 15-1 was replaced by an appropriate isotype antibody. Ultrathin sections were cut using an "Ultracut" ultramicrotome (Reichert Scientific Instruments, Buffalo, NY) and examined with an electron microscope (1200 XL; Jeol, Tokyo, Japan).

## RESULTS AND DISCUSSION

In the present study, we investigated the immunophenotypic and morphologic features of FcεRIα-bearing cells within the human dermis, aiming to clarify their ontogenetic derivation and to define their relationship to different cell lineages. In a first series of experiments, we confirmed our previous findings [1] i) that MoAb 15-1, directed against the α-chain of FcεRI, reacts with dendritic cells in the dermis, ii) that these FcεRIα$^+$ cells are predominantly located in the papillary dermis in close proximity to the capillaries of the superficial vascular plexus, and iii) that approximately one third (35% ± 21%) of all dermal FcεRIα$^+$ cells, particularly those located in the deeper part of the tissue, react with avidin-FITC, and thus, represent mast cells [4] (Fig 1). Although approximately one third (33% ± 31%) of all avidin-FITC$^+$ mast cells displayed clear 15-1 immunoreactivity, the majority of the cells showed only faint and, sometimes, barely visible 15-1 positivity. On a quantitative basis, FcεRIα-bearing cells of the mid and upper dermis were now found to exhibit a density of 32 ± 9 positive cells/mm$^2$.

To unravel the nature of the FcεRIα$^+$ non-mast cells within the human dermis, we performed immunofluorescence double-labeling experiments using a panel of lineage specific antibodies (Table I).

The results obtained (Table II) showed that virtually all (98% ± 5%) FcεRIα$^+$ cells in the dermis express CD45, which proves their bone marrow origin [12].

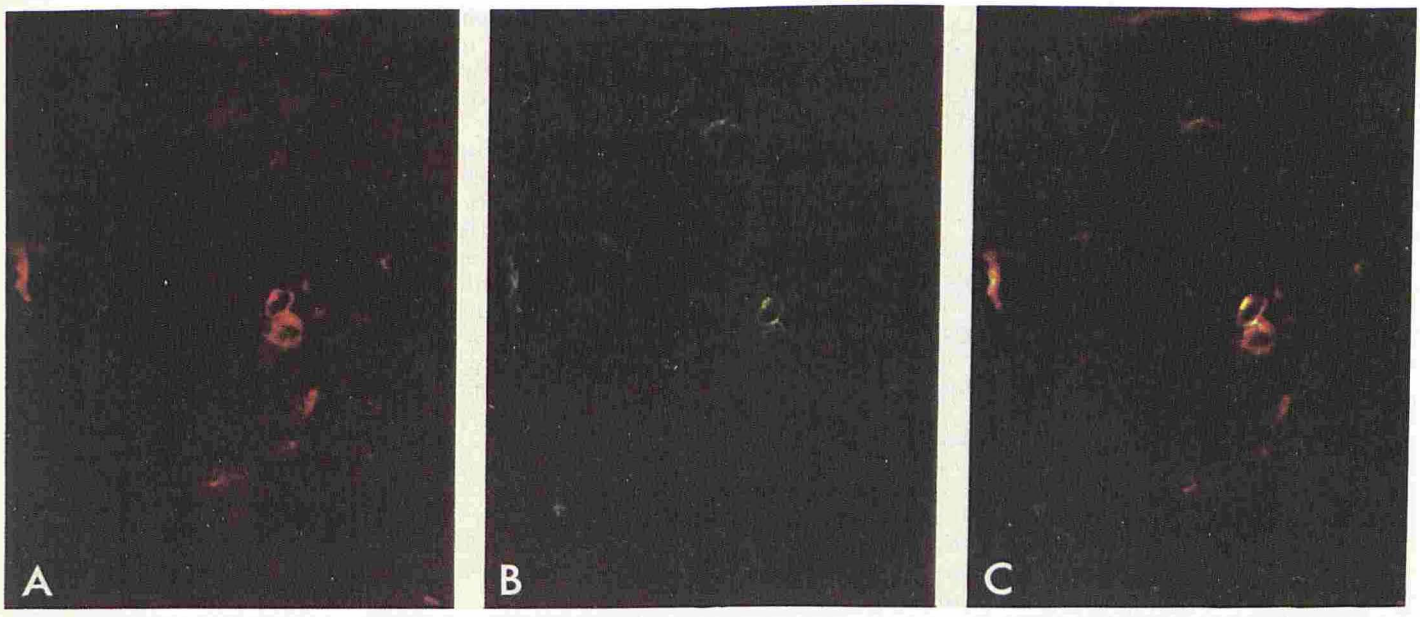


**Figure 2.** Demonstration of CD1a on a portion of FcεRIα$^+$ dermal cells. Cryostat sections were reacted with MoAb 15-1/Texas Red and counterstained with MoAb OKT6-FITC. Single photographic exposure of an identical field with the appropriate filter shows FcεRIα$^+$ cells in red *(A)* and CD1a$^+$ cells in green *(B)*. Double photographic exposure reveals that some dermal cells appear yellow or orange due to their reactivity with MoAb 15-1 and MoAb OKT6 *(C)*, indicating that dermal LC express FcεRIα. *Bar*, 24 μm.

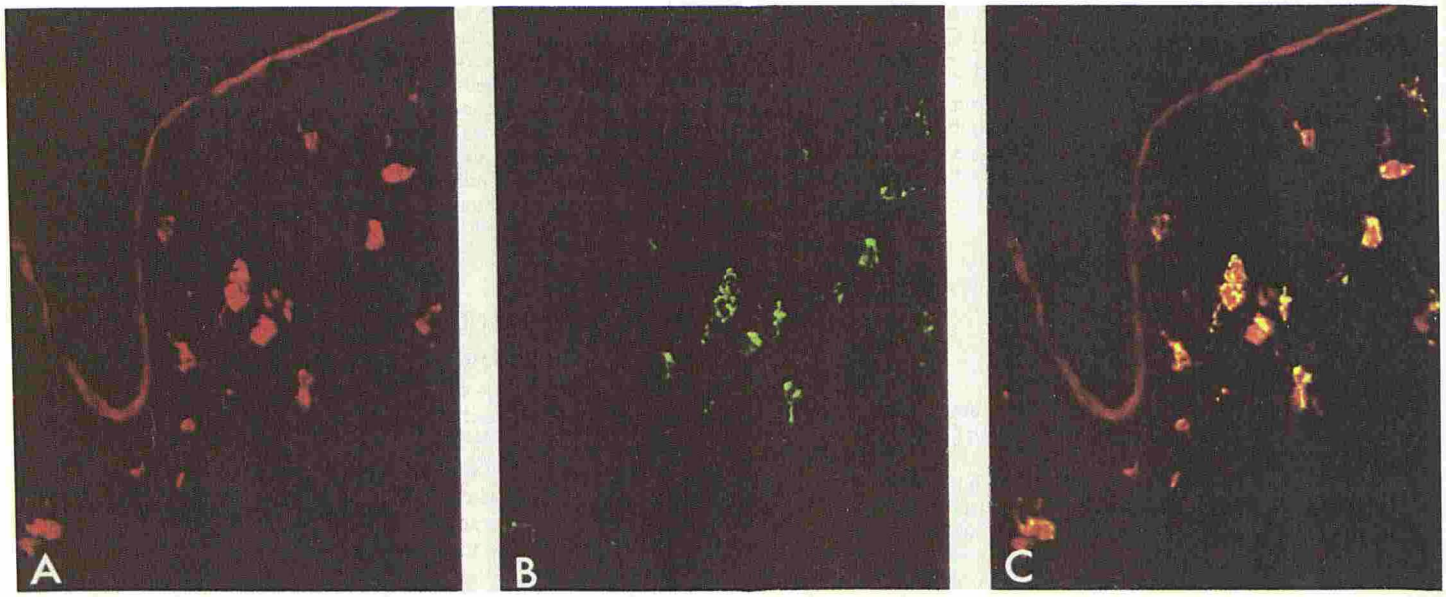


**Figure 3.** Demonstration of RFD1-reactive moieties on a major portion of FcεRIα$^+$ dermal cells. Cryostat sections were reacted with MoAb 15-1/Texas Red and counterstained with MoAb RFD1/FITC. Single photographic exposure of an identical field with the appropriate filter shows FcεRIα$^+$ cells in red *(A)* and RFD1$^+$ cells in green *(B)*. Double photographic exposure reveals that the majority of dermal cells appear orange due to their reactivity with MoAb 15-1 and MoAb RFD1 *(C)*, indicating that cells of the LC/DC lineage express FcεRIα. *Bar*, 49 μm.

Our further observations i) that CD3 antigens and FcεRIα are expressed on mutually exclusive cell populations and ii) that the human dermis is devoid of CD19$^+$ and CD15$^+$ cells, lead us to conclude that neither T cells, B cells, nor granulocytes [13] significantly contribute to the pool of FcεRIα$^+$ dermal cells.

To investigate the relationship between FcεRIα$^+$ dendritic cells of the upper dermis and cells of the LC/DC-lineage, we performed immunofluorescence experiments using MoAb 15-1 versus either MoAb OKT6 (anti-CD1a) expressed on resident LC [14], RFD1 expressed on interdigitating cells of the LC/DC lineage [10], or anti-HLA-DR expressed on all cells of the LC/DC lineage [15]. Results obtained (Table II) showed that 14% ± 8% of all 15-1$^+$ cells expressed CD1a (Fig 2) and, conversely, that most (82% ± 21%) CD1a$^+$ cells display 15-1 reactivity. Further, we found that the vast majority of FcεRIα$^+$ dermal cells express both HLA-DR (84% ± 13%) and RFD1-reactive moieties (72% ± 23%) (Fig 3) indicating that most FcεRIα$^+$ cells belong to the LC/DC lineage. In reverse fashion, approximately two thirds (70% ± 13%) of all RFD1$^+$ cells

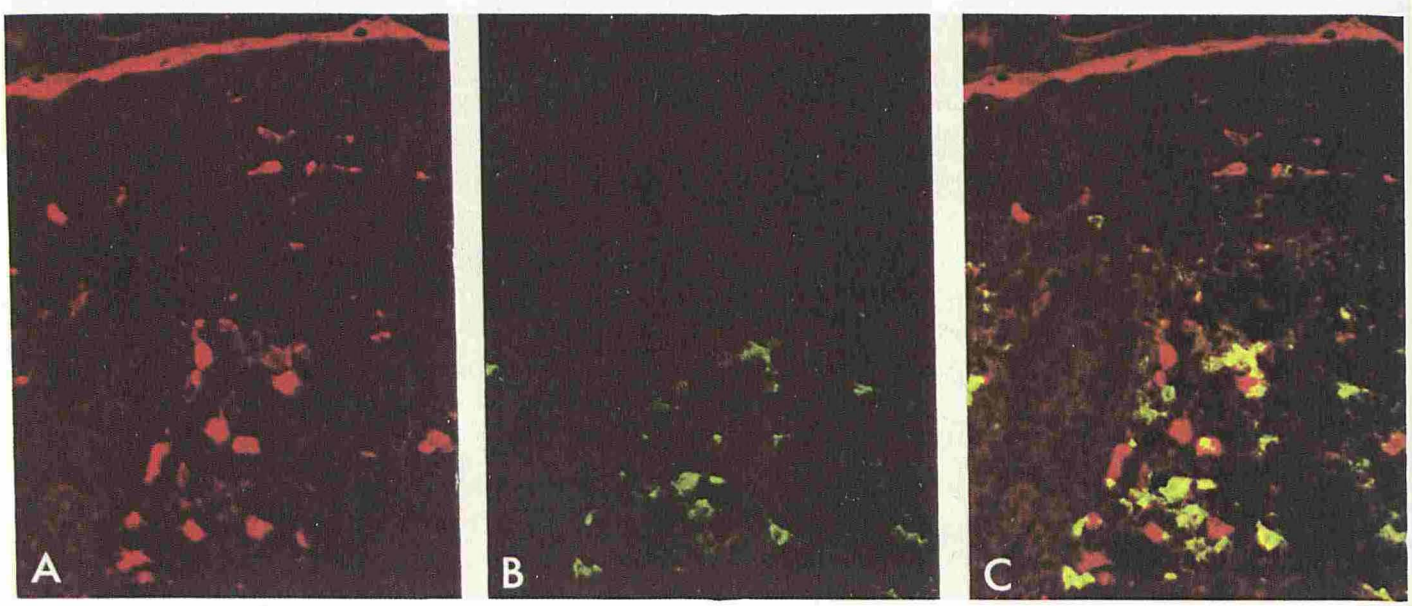


**Figure 4.** FcεRIα$^+$ cells and FXIIIa$^+$ cells are mutually exclusive cell populations. Cryostat sections were reacted with MoAb 15-1 visualized with Texas Red and with rabbit antibody against FXIIIa visualized with FITC. Single photographic exposure of an identical field with the appropriate filter shows FcεRIα$^+$ cells in red *(A)* and FXIIIa$^+$ cells in green *(B)*. Double photographic exposure reveals that red and green cells show essentially no overlap *(C)*, indicating that FXIIIa$^+$ macrophages do not express FcεRIα. *Bar*, 49 μm.

**Table III.** Leukocyte Differentiation Antigens Expressed on Cells of the LC/DC-Lineage (percentage ± SD)

| Dermal LC ($CD1a^+$) | Indeterminate Cells ($CD1c^+$) | Interdigitating Cells ($RFD1^+$) |
|---|---|---|
| | 27% ± 23% $CD1a^+$ | 17% $CD1a^+$ (n = 3) |
| 100% ± 1% $CD1c^+$ | | 39% ± 14% $CD1c^+$ |
| all cells $RFD1^+$ (n = 3) | 76% ± 17% $RFD1^+$ | |

expressed FcεRIα. Our further observations (Table III) that i) all CD1a-bearing dermal dendritic cells coexpress CD1c (an antigen found on indeterminate cells, defined as cutaneous, dendritic nonkeratinocytes lacking Birbeck granules, melanosomes, or Merkel cell granules [16]), and moieties recognized by MoAb RFD1, and ii) that CD1c-expressing and RFD1-expressing cell populations are largely overlapping, implies that most, if not all, dermal cells of the LC/DC lineage express FcεRIα. However, it should be mentioned that CD1a/CD1c expression by $FcεRIα^+$ cells is not an unequivocal proof for their affiliation to the LC/DC lineage because recent *in vitro* studies [17–19] showed that CD1 can be expressed by peripheral blood monocytes cultivated in the presence of GM-CSF [17], GM-CSF and IL-4 [18], or low concentrations of fetal bovine serum (FBS) [19].

To clarify the relationship between $FcεRIα^+$ cells and mononuclear phagocytes we performed double-labeling experiments using MoAb 15-1 and rabbit antibody directed against FXIIIa expressed by dermal dendrocytes [6–8]. On the basis of their phenotypic profile ($CD36^+$, $CD11b^+$, $CD14^+$, $CD1^-$ [6,7], $CD68^+$ [8]), these cells are considered to belong to the mononuclear phagocyte lineage. Our results showed that the expression of FcεRIα and FXIIIa is mutually exclusive (Fig 4). Together with the finding that most (91% ± 13%) of the $FXIIIa^+$ cells react with the pan-macrophage marker KiM8 [20,21] (Table IV) this observation implies that a substantial portion of dermal macrophages are devoid of immunohistologically detectable FcεRIα moieties. Unfortunately, we could not directly address this issue because the MoAb, KiM8 and 15-1, are both of the $IgG_1$ isotype and can therefore not successfully be used for double-staining purposes. We found, however, that 50% ± 25% of all $RFD1^+$ cells in the dermis react with MoAb KiM8 (Table IV). Based on the fact that most $RFD1^+$ dermal cells display 15-1 reactivity (see above) one must therefore assume that at least a subpopulation of the $KiM8^+/RFD1^+$ cells express FcεRIα. Although the reactivity with KiM8 is compatible with the view that this $FcεRIα^+$ subpopulation belongs to the macrophage family, our recent finding of KiM8 expression on $CD1a^+$ epidermal and dermal cells (Osterhoff *et al,* unpublished observations) questions the selectivity of KiM8 as macrophage marker and opens the possibility for the existence of a $RFD1^+/CD1a^-/KiM8^+$ member of the LC/DC lineage. Immunoelectronmicroscopic experiments supported this conclusion because the majority of $FcεRIα^+$ cells—although devoid of Birbeck granules—have a folded, or even indented, nucleus, a high number of mitochondria and endo-/lysosomal structures, a moderately well-developed Golgi apparatus, and a rough endoplasmatic reticulum, and fail to exhibit granules specific for basophils or eosinophils (Fig 5) [22].

**Table IV.** Leukocyte Differentiation Antigens Expressed on Different Cell Types (percentage ± SD)

| Dermal Dendrocytes ($FXIIIa^+$) | Macrophages ($KiM8^+$) | Interdigitating Cells ($RFD1^+$) |
|---|---|---|
| | 44% ± 17% $FXIIIa^+$ | ND |
| 91% ± 13% $KiM8^+$ | | 50% ± 25% $KiM8^+$ |
| ND[a] | 18% ± 6% $RFD1^+$ | |

[a] ND, not determined.

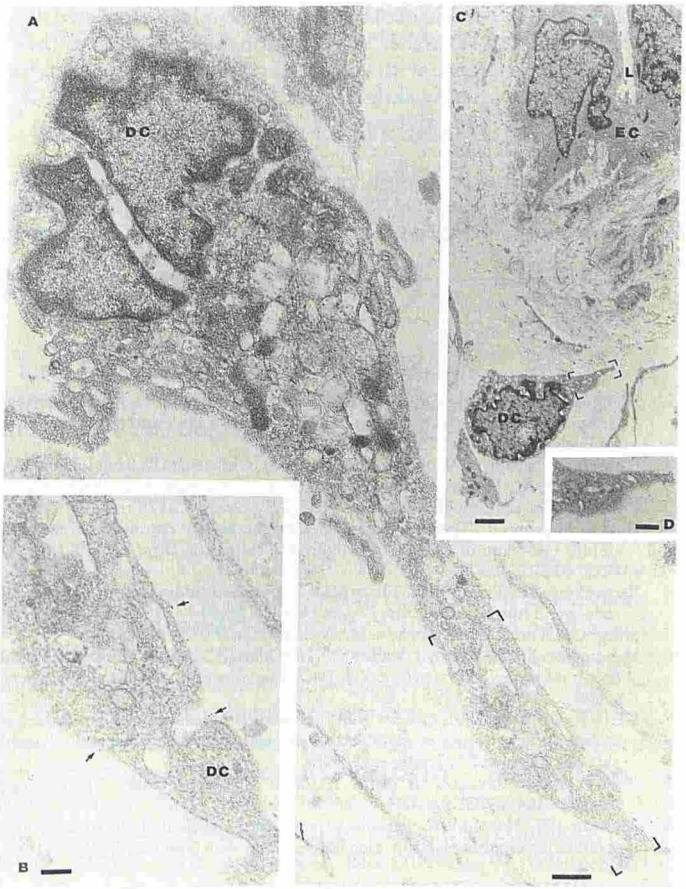


**Figure 5.** Ultrastructural characterization of $15\text{-}1^+$ non-mast cells within the human dermis, processing a preembedding immunogold technique. FcεRIα-bearing cells exhibit either long and spindle-shaped cytoplasmic dendrites or short and blunt cell processes *(A,C)*. They have an indented, or even folded, nucleus that may occasionally appear segmented *(A)*. Within their cytoplasm these cells contain large numbers of endo-/lysosomal structures *(A)*. Most $15\text{-}1^+$ non-mast cells are localized in close proximity to blood vessels *(C)*. *B* and *D* show in higher magnification the areas indicated by brackets in *A* and *C*: note that FcεRIα, as indicated by MoAb 15-1 and 5-nm gold particles, is uniformly expressed on the entire surface of the dendritic cells *(arrows)*. DC, dendritic cell; EC, endothelial cell; L, lumen. Magnifications: *A*, ×17,000; *bar,* 0.5 μm. *B*: ×30,000; *bar,* 0.25 μm. *C*: ×7,000; *bar,* 1 μm. *D*: ×20,000; *bar,* 0.3 μm.

This study therefore demonstrates that a major portion of dermal FcεRIα-bearing, non-mast cells belong to the LC/DC lineage. Whether these cells are in transit to or from the epidermis or shun the epidermis entirely has yet to be answered. Romani *et al* [23] found that LC, cultured for 2–4 d, strongly react with MoAb RFD1. Because cultured LC resemble lymphoid DC in many other phenotypic and functional aspects, one may assume that dermal $FcεRIα^+/RFD1^+$ cells represent LC emigrating from the epidermis. On the other hand, our observation that cytokine-activated LC rapidly downregulate FcεRIα (Maurer *et al,* unpublished observation) contradict this argumentation.

Concerning the possible function of FcεRI it should be remembered that patients with hyperimmunoglobulinemia E [24], in particular atopic dermatitis patients [25], have a distribution pattern of $IgE^+$ cells similar to that of $FcεRIα^+$ cells observed in our studies ([1], this study). This is compatible with the view that FcεRIα is the major IgE-binding structure in this disease. If this should be the case, crosslinking of IgE by antigens may be followed by receptor-mediated transmembrane signaling resulting in either secretion of various soluble factors and/or internalization of the antigens followed by antigen processing and presentation and, finally, by an

elicitation of a major histocompatibility complex–restricted immune response [26]. If further investigations should confirm these speculations, interference with the FcεRI could be a mechanism for the suppression of allergic skin diseases.

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